Short reports

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Child with a defect in leucine metabolism associated with β -hydroxyisovaleric aciduria and β -methylcrotonylglycinuria

Three inborn errors of the leucine degradation pathway are known, maple syrup urine disease, isovaleric acidemia, and β -methylcrotonylglycinuria. The latter was first described by Eldjarn and his colleagues in 1970 (Eldjarn *et al.*, 1970; Stokke *et al.*, 1972). The patient they reported excreted large amounts of β -methylcrotonylglycine and β -hydroxyisovaleric acid, presumably due to a defective activity of the enzyme β -methylcrotonyl CoA carboxylase. A second child with these metabolites in his urine was described the following year (Gompertz *et al.*, 1971). The clinical presentations of these two children were entirely different. The first suffered from a neurological condition similar to Werdnig-Hoffmann disease, while the second presented with vomiting and an acute metabolic acidosis and ketosis. In this report we describe a 9-month-old infant who was admitted moribund with an upper lobe pneumonia and was subsequently shown to be excreting these abnormal metabolites.

Case report

A 9-month-old child of first-cousin Pakistani parents was admitted with a history of severe respiratory difficulty for 6 hours. 2 days before admission he was noted to be lethargic and febrile, and he was prescribed aspirin and penicillin. On admission he appeared moribund, with constricted pupils. Temperature 39 °C. Respiratory rate was only 12/min, heart rate 100/min. He was not cyanosed. There was slight intercostal recession and on auscultation there were widespread crepitations and rhonchi. Chest x-ray showed a left upper lobe pneumonia. Blood gases in oxygen were P_{O_2} 250 Torr and P_{CO_2} 81 Torr; pH 7.2. Preliminary investigations included Hb, white cell count, CSF, urea, electrolytes, and blood sugar, and all were normal.

At and following birth he had been normal. One month before admission he had been seen because of recurrent upper respiratory tract infections, and a delay in motor development was noted. There had been one female sib; she had congenital heart disease and died at 10 months, the cause of death not known.

He was treated with penicillin, kanamycin, and hydrocortisone. Though blood gases returned to normal within 12 hours, his state of consciousness remained poor. Since lobar pneumonia alone seemed an inadequate explanation, screening tests for metabolic disease and poisoning were undertaken with these results. Urinary ketones, amino acids, and coproporphyrins, and blood lead and barbiturate levels were all normal. Careful inquiries of the parents showed no access to other poisons, in particular opiates. However, screening for urinary organic acids showed abnormal amounts of β -hydroxyisovaleric acid and β -methylcrotonic acid present. Treatment with biotin (5 mg twice daily orally) was then begun.

His clinical state gradually improved over the next 4 days and his level of consciousness, which had fluctuated throughout this period, returned to normal. Assessment 4 weeks after admission showed no localizing neurological signs, though there was some pallor of both optic discs. He was, however, obviously developmentally retarded.

Biochemical studies

Urine samples collected on the first 3 days of admission were screened for organic acids using gas chromatographic procedures (Gompertz and Draffan, 1972a). Volatile fatty acids were analysed on a neopentylglycol adipate-phosphoric acid column. Other organic acids and glycine-conjugates were analysed as their methylated derivatives on a polyester column. All three urine samples contained β -hydroxyisovaleric acid, β -methylcrotonic acid, and β -methylcrotonylglycine in abnormal amounts. The identity of β -hydroxyisovaleric acid and β -methylcrotonylglycine was confirmed by mass spectrometry (Gompertz and Draffan, 1972b).

The presence of these three metabolites suggested an impaired β -methylcrotonyl CoA carboxylase activity. This enzyme is biotin dependent and the previous child reported by us (Gompertz *et al.*, 1971) responded to massive doses of biotin. A further urine sample was collected, following which biotin 5 mg twice daily was given orally. Quantitation of the three metabolites was then performed (Fig. 1). Before biotin administration was granted, the concentration of β -hydroxyisovaleric acid in the urine had fallen from 5.5 mmol/l. to 0.5 mmol/l., and there was improvement in the child's clinical status. From the ninth day onwards the trace amounts of β -hydroxyisovaleric acid and β -methylcrotonic acid in the urine were within the normal range.

Ten days after stopping biotin therapy, the patient was given 100 mg L-leucine/kg body weight. Timed urine samples during the next 24 hours were collected. The sample collected between 2 and 4 hours after the loading

FIG. 1.—Urinary concentrations of β -hydroxyisovaleric acid (β HOIVA), β -methylcrotonic acid (β MCA), and β -methylcrotonylglycine (β MCG).

test contained increased concentrations of β -hydroxyisovaleric acid and β -methylcrotonic acid, both in absolute terms (Fig. 1) and in relation to creatinine excretion (Fig. 2). Similar results were obtained from another loading test performed one week later.

FIG. 2.—Leucine loading test: β -methylcrotonic acid (β MCA) concentration in relation to creatinine concentration during the loading test.

After discharge from hospital his parents took him to Pakistan for 6 months. During this period he received no biotin nor any multivitamin preparation, but he

remained well. On his return he was found to be excreting abnormal amounts of β -methylcrotonic (0.10–0.24 mmol/l.) and β -hydroxyisovaleric acids (1.1 mmol/l.). Treatment with biotin 10 mg twice daily orally brought the excretion of these metabolites back to normal levels within 48 hours.

Discussion

This patient at presentation was moribund with a respiratory acidosis. The severity of his clinical state seemed out of proportion to the respiratory infection. The finding of the three metabolites of β -methylcrotonyl CoA in the urine of this patient indicated an impairment of β -methylcrotonyl CoA carboxylase (Stokke *et al.*, 1972).

In the first child reported with this condition the metabolites were continually present in the urine from diagnosis to death at 9 months of age (Stokke *et al.*, 1972). The second child excreted the same group of metabolites until he was started on biotin therapy (Gompertz *et al.*, 1971). The patient described here excreted large amounts of β -hydroxyisovaleric and β -methylcrotonic acids during the first few days of his illness. Treatment of his respiratory infection was followed by a rapid fall in the excretion of the three metabolites of β -methylcrotonyl CoA. Biotin therapy was also started during this period and the excretion of β -methylcrotonic acid and β -hydroxyisovaleric acid became normal. During the next 6 months he received no additional biotin, and the excretion of these urinary metabolites returned to the abnormal levels seen during the leucine loading tests. The return of these metabolites in the absence of biotin therapy together with the effects of a second course of biotin treatment shows that this child had a biotin-responsive form of this inborn error of metabolism.

The three children described with presumed β -methylcrotonyl CoA carboxylase deficiencies had different proportions of the three metabolites in their urine, and different clinical presentations. Further experience of patients excreting these metabolites will be necessary before the relation between the enzymic disturbance and the range of clinical presentations can be established.

Summary

A 9-month-old boy presented with pneumonia and in semi-coma. He was shown to be excreting β -hydroxyisovaleric acid, β -methylcrotonic acid, and β -methylcrotonylglycine, all being metabolites of β -methylcrotonyl CoA. On treatment of the pneumonia and after administration of biotin, his neurological state improved and the abnormal metabolites disappeared from his urine, however

their excretion could be provoked later by leucine loading tests. After 6 months without biotin therapy, excretion of the abnormal metabolites recurred, but again stopped within 48 hours after biotin therapy.

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Diaphragmatic paralysis in the newborn

Paralysis of the hemidiaphragm resulting from injury of the phrenic nerve is considered to be a rarity in the newborn infant (Schaffer and Avery, 1971), though 3 such cases were found among 1671 consecutive deliveries (Cavrot and Richard, 1957), and an earlier search of published reports provided another 74 cases (Richard *et al.*, 1957). It seems likely that diaphragmatic paralysis occurs with greater frequency than is reported, partly because symptoms vary so much in severity. Thus mild transient cases may not attract attention as in the case reported by Smith (1972). On the other hand, in severer cases other diagnoses such as congenital heart disease are incorrectly made, as in the case reported by Adams and Gyepes (1971) where severe cyanosis led to heart catheterization and angiography being performed because the newborn

was erroneously thought to have severe cyanotic congenital heart disease.

The 3 cases of unilateral paralysis of the diaphragm described here illustrate the wide spectrum of the clinical manifestations. The first baby had only mild respiratory distress and the diagnosis was only made at age 3 months; the second presented with the classical clinical picture of this condition; in the third baby cyanosis was sufficiently severe to mimic congenital heart disease.

Case reports

Case 1. A 3-month-old male was admitted because of mild respiratory difficulty. He was born at another hospital to a 37-year-old primipara primigravida. The infant was a breech presentation and at 36 weeks a forceps extraction was reported to have been 'difficult'. Birthweight was 2910 g. Immediately after birth the infant was tachypnoeic and cyanotic and he failed to use his left arm. He was placed in an incubator and was given oxygen. At 36 hours a chest x-ray showed nothing abnormal. Thereafter he improved and, in spite of slight persisting tachypnoea, he was discharged at 15 days. From then until the day he was admitted to our department he had mild respiratory difficulty and two episodes of 'bronchopneumonia'.

On admission at the age of 3 months the baby was slightly tachypnoeic but otherwise comfortable. The Erb's palsy had disappeared completely. Breath sounds were absent over the lower half of the left chest. Chest x-ray showed elevation of the left hemidiaphragm (Fig.).

FIG.—Case 1. Elevation of the left hemidiaphragm and mediastinal shift to the right.

Fluoroscopy showed paradoxical movement of the left side of the diaphragm and exaggeration of the mediastinal shift to the right on expiration.

The baby was observed for several days; symptoms other than mild tachypnoea were absent, so he was discharged. He was readmitted at 5 months because he was still tachypnoeic. Chest x-ray was almost identical to that taken 2 months previously. Surgical plication